Remarks

Claims 1-42 are pending. Claims 1, 2, 9, 17, 19, 21, 23, 25, 32, 34, and 36 have been amended.

Rejection Under 35 U.S.C. § 112, first paragraph

A. Claims 1-42 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

1. The present rejections appear to be primarily based on the use of the phrase "infectious particles having a characteristic of AAV." For example, the Examiner has stated that "it is unclear how one of skill in the art could possibly know what are the characteristics of AAV4" and "the recombinant vector system as claimed has been defined only by a statement of function that broadly encompasses having any and all characteristics of AAV4." However, the Applicants are not claiming any vector system having a characteristic of AAV4, but rather a vector system wherein at least one vector comprises a nucleic acid encoding an AAV4 capsid protein. Such a vector system will inherently have a characteristic of AAV4 based on the expression of at least this protein.

It should be pointed out that the instant disclosure was the first demonstration of an AAV other than AAV2 to function as a vector for gene transfer. Furthermore, there have been several reports describing AAVs with poor transduction and/or packaging activity. Therefore, one of skill in the art could not have predicted the ability of AAV4 to be used as a vector in a vector system prior to the present disclosure. In contrast, the instant disclosure was sufficient to enable one of skill in the art to prepare a vector system having the desired tissue tropism of AAV4. For example, it is explicitly taught in the specification (pg. 42, line 17) that it is the differences in capsid proteins that are relevant to the differences in hemagglutination and tissue tropism between AAV4 and other adeno-associated viruses (AAVs). Furthermore, based on applicants publications regarding the distinctions between AAV4 and AAV2, it is generally accepted by those skilled in the art that the capsid proteins of AAV vectors are the elements that would convey these characteristics.

AAV capsids utilize different cell surface carbohydrates for cell binding and entry, which are at least partly responsible for differences in AAV cell transduction phenotypes. For example, Heparan sulfate proteoglycans (HSP) have a role in the cell association and transduction of AAV2, however transduction with AAV4 and AAV5 serotypes does not appear to utilize HSP (Chiorini, J.A., *et al.* 1999. J Virol. 73(2):1309-19, **reference attached**). Furthermore, it is the basic residues in the capsid protein VP3 that are responsible for the interaction of AAV2 with heparan sulfate proteoglycans (Kern, A., *et al.* 2003. J. Virol. 77:11072-11081; Opie, S.R., *et al.* 2003. J. Virol. 77:6995-7006, **references attached**). Likewise, AAV4 and AAV5 have hemagglutination activity that is dependent upon unique sialic acid binding of the capsid proteins (Kaludov, N, *et al.* 2001. J. Virol. 75:6884:6893, **reference attached**). Therefore, the Applicants submit that one of ordinary skill in the art would recognize that the AAV4 capsid proteins are what contribute to the unique properties of AAV4.

Thus, in order to facilitate prosecution, the Applicants have amended Claim 1 to delete the phrase "having a characteristic of AAV4." This phrase was also omitted in Claim 2, which the Applicants have amended to be an independent claim. Support for this amendment can be found at least in Claims 1 and 2 as filed. It is believed that these amendments do not constitute new matter. The Applicants therefore respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner has also indicated another basis for the present rejection. Specifically, the Office action states that, while the scope of the invention encompasses variants of AAV4 Rep and capsid proteins that are only 95-98% identical to the disclosed representative proteins, the specification allegedly "fails to disclose variants of AAV4 Rep and capsid proteins." The Examiner appears to be positing that the specification has not provided adequate description of the genus of proteins encompassed by the sequence homologies. However, the USPTO has already established that variants can be claimed based on sequence identity (see Example 14 of the U.S.P.T.O. "Synopsis of Application of Written Description Guidelines"), wherein it is stated:

> "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of

> the presence of an assay which applicant provided for identifying all of the at least 95% identical variants...which are capable of the specified catalytic activity." (page 54, fourth paragraph)

In the case of AAV4 Rep and capsid variants, it is routine experimentation for one skilled in the art to test such variants to determine if they fit into the claimed homology. It is also routine to assay AAV4 Rep and capsid variants for functionality by, for example, assaying the ability of a vector system to replicate and produce encapsidated particles, respectively. Such methods are clearly known in the art and exemplified in the specification. Each of claims 17, 19, 21, 23, and 25 have been amended to include the functional limitation "wherein the vector system replicates." Support for these amendments can be found at least on page 1, lines 25-28. Each of claims 32, 34, and 36 have been amended to include the functional limitation "wherein the vector system produces AAV particles." Support for these amendments can be found at least on page 2, lines 15-23 and in the Examples where infectious encapsidated AAV particles are produced. For at least these reasons, the specification clearly provides adequate written description of the claimed variants of AAV4 Rep and capsid proteins. The Applicants therefore respectfully request the withdrawal of this rejection.

B. Claims 1-42 were also rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. For the reasons stated above, the Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 9 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Office action notes a typographical error wherein a space between two words was omitted. Claim 9 has been amended to correct this error.

Rejection Under 35 U.S.C. § 102

Claim 1 was rejected under 35 U.S.C. § 102(b) as being anticipated by Muster et al. (Virology 35(3):653-61, 1980). According to the Office Action, the instant claims are drawn to a nucleic acid encoding an AAV4 capsid protein. Muster et al. teaches isolation of AAV4 DNA and physical mapping of the AAV4 genome. Muster et al. also teaches isolation of AAV4 virions from the host cells, followed by isolation of AAV4 DNA from the purified virions. The Office

Action states that the cited art clearly anticipates the invention as claimed because the composition and functions as claimed are presumed inherent in the prior art regarding AAV DNA. Further stated in the Office Action is that since the composition is physically the same, it must have the same properties.

Applicants respectfully point out to the Examiner that the instant claims are not to "a nucleic acid" but instead are to a "vector system" wherein at least one vector comprises a nucleic acid encoding an AAV4 capsid protein. Muster et al. does not teach a vector system, and therefore, does not anticipate claim 1. The disclosure of the existence of AAV4 in Muster et al. did not provide a basis for expecting that it could be used as a vector in a vector system as described and claimed by applicants in the present application. In fact, Muster et al. provides no AAV4 sequences, thus providing no chemical structure for any AAV4 sequence. In order to utilize the AAV4 genome and its subsequences as vectors, it was necessary to isolate and sequence an exemplary AAV4 genome to determine whether or not it could be used as a vector. It was not until the Applicants sequenced and identified the relevant characteristics of the AAV4 genome that one could have known that AAV4 had properties that would make it useful as a vector or that it would have characteristics distinct from other types of AAVs that would give it advantages over other AAV vectors. Although Muster et al. teaches the isolation of virions that comprise the AAV4 genome, Muster et al. provides no chemical structures, i.e. AAV4 sequences, or indications of what chemical structures may exist or how to utilize them as a vector.

Instead, Muster et al. (J. Virol., 35(3): 653-661, Sept. 1980) disclosed that AAV had only one size of message, unlike AAV2, which has multiple messages that would be expected to encode multiple proteins. At a minimum, this reference showed that AAV4 has a different genomic organization than AAV2. At the time of Muster et al.'s publication and at the time of the present invention, AAV2 was the only AAV that had been known to be useful as a vector. Given this basic structural divergence between AAV2 and AAV4 as shown in Muster et al., one of skill would not have believed that the ITRs or other components would be the same. Since it is the structure of the components that determines whether the virus will work as a vector, Muster et al. provides a basis to believe that AAV4 would not work as a vector. Thus, the

teachings of Muster et al. would not have led one of skill in the art to identify useful sequences and would, in fact, have led one away from identifying useful AAV4 sequences.

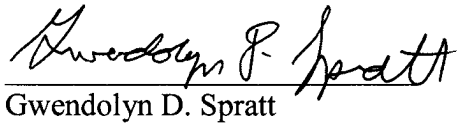
However, in order to facilitate prosecution and more clearly claim what the Applicants consider to be their invention, Applicants have amended Claim 1 to recite "isolated nucleic acid encoding an AAV4 capsid protein." Support for this amendment can be found at least on page 5, lines 31-32, and page 15, lines 30-33. The plain meaning of the term "isolated" indicates that the nucleic acid must be separated from something in its natural state, i.e., must not comprise the entire AAV4 genome. Accordingly, there is no evidence that Muster et al. taught an isolated nucleic acid encoding an AAV4 capsid. Neither did Muster et al. teach a vector, or even a virion, comprising less than the entire AAV4 genome. Thus, Claim 1 as amended is not anticipated by Muster et al. The Applicants therefore believe this rejection has been overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

It is believed that no fee is due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



Gwendolyn D. Spratt
Registration No. 36,016

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)